UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,781	06/10/2005	Chikamasa Yamashita	04676.0186-00000	9421

22852 7590 07/10/2009

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
07/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,781	YAMASHITA ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *15-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending. Applicants amended claims 1-6 and 14. Claims 15-24 are withdrawn for being drawn to a non-elected invention. **Claims 1-14 are under examination in the instant office action**. Receipt of Applicants' amended claims and remarks/arguments submitted on April 21, 2009 and supplemental response and 1.131 declaration submitted on April 23, 2009 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Election/Restrictions

Applicant's election of Group I, claims 1-14, in the reply filed on 5/22/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 15-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse[1] in the reply filed on 5/22/08.

Priority

Receipt of Applicants' certified English langauge translation of the foreign priority document, JP 2002-363026, is acknowledged, which had been placed of record in the file.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

---

[1] Applicants' response was silent as to whether the election was with or without traverse. Thus, the election was treated as an election without traverse.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP-61044826 ("JP-826"), wherein Akagi et al. (EP 0168008) ("Akagi") is provided as an English language equivalent, in view of JP 59-181224 (English Abstract only; IDS reference; "JP-224") and Tober et al. ("Structural features of interferon-gamma aggregation," Protein Science, 2002 June, 11(6), 1340-1352).

Note: Additional relevant citations to the English language equivalent of JP-826 are set forth below and are designated as Akagi. An English language translation of JP-224 is included with the instant office action.

Applicant Claims

Applicants claim a freeze-dried composition comprising (i) interferon-gamma, (ii) at least one hydrophobic stabilizer selected from a group including hydrophobic amino acids and derivatives of hydrophobic amino acids, and (iii) at least one hydrophilic stabilizer selected from the group including hydrophilic amino acid derivatives.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

JP-826 teaches a **freeze-dried interferon-gamma composition** comprising an amino acid (e.g. **monoamino-aliphatic amino acid**) having a decreased inorganic salt concentration (preferably below 0.05M). The term "monoamino-aliphatic amino acid" reads on hydrophobic amino acids. Per Applicants' definition in paragraph [0110] of the specification, any freeze-dried interferon-gamma composition necessarily has a non-powder cake-like form.

It is art recognized that gamma-interferon is very unstable and its aqueous solutions easily decrease in activity during storage or during the process of freezing or lyophilization, thus, necessitating the inclusion of stabilizers (Akagi: pg. 1, 1st paragraph). **Preferred amino acid stabilizers are monoamino aliphatic amino acids, such as glycine, alpha-alanine, beta-alanine, leucine (i.e. a hydrophobic stabilizer), glutamic acid (i.e. a hydrophilic stabilizer), or aspartic acid (i.e. a hydrophilic stabilizer)**, which may be used singly **or in combination of two or more amino acids** (Akagi: pg. 5, 1st full paragraph on said page). The total amino acid amount is preferably not less than 1 mg, more preferably 5-50 mg/ml of aqueous interferon-gamma solution (Akagi: pg. 5, 2nd paragraph). **Akagi teaches a general procedure for obtaining lyophilized interferon-gamma formulations** from page 7, last full paragraph through page 9, 1st full paragraph.

JP-224 teaches stabilized freeze-dried interferon preparation comprising human serum albumin and an amino acid, wherein the **human serum albumin is present in an amount of 0.01% w/v** and **the amino acid is preferably present in an amount of 0.05% w/v**. JP-224 teaches that any amino acid can be used, but that particularly effective amino acids include polar amino acids, such as arginine, lysine, serine, threonine, etc. Per Applicants' definition in paragraph [0110] of the specification, any freeze-dried interferon-gamma composition necessarily has a non-powder cake-like form.

Tober teaches that interferon-gamma is susceptible to denaturing and aggregation under a variety of conditions, such as high temperature, low pH, and in the presence of chaotropes (pg. 1341, right column, 1st full paragraph in right column).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

JP-826 lacks the teaching of freeze-dried interferon compositions comprising hydrophilic stabilizers. This deficiency is cured by the teachings of JP-224. JP-826 is silent regarding the teaching of a disintegration index and the effect of an air impact with a speed of at least 1 m/sec and an air flow rate of at least 17 ml/sec.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to combine the teachings of JP-826 and JP-224 at the time of Applicants' invention, because interferon-gamma is known to be unstable under various conditions (Tober). An ordinary skilled artisan would have been motivated to include serum albumin and amino acid stabilizers in the formulation of JP-826 to stabilize interferon-gamma, because interferon gamma is known to be susceptible to denaturation under various conditions. An ordinary skilled artisan would have had a reasonable expectation of stabilizing interferon-gamma in the formulations of JP-826, because JP-224 teaches that amino acids in combination with serum albumin result in stabilized interferon preparations. Regarding the disintegration index, because the combined prior art teach substantially similar composition to what Applicants' are claiming this property is necessarily present. It is also noted that the term disintegration index is not a term of art in the pharmaceutical art, but rather is a term invented by Applicants and defined in paragraph [0112] of Applicants' disclosure. It is noted that serum albumin reads on a derivative of any amino acid, including hydrophobic amino acid derivatives, which are kind of hydrophobic stabilizer recited in Applicants' claim 1. The ratio of serum

albumin and amino acid recited in JP-224 falls within the range of the ratio recite in Applicants' claim 8. In addition, the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Upon optimization of the amounts of albumin and amino acid, the compositions of the prior art would optimize the ratio of hydrophilic and hydrophobic stabilizers.

Regarding property (iv) of Applicants' claim 1 and Applicants' dependent claims 11-13, this property is necessarily present because the combined prior art teaches essentially the same formulation claimed by Applicants. Thus, it is a reasonable to conclude that property (iv) is present in the formulations of the combined prior art. Finally, concerning the selection of valine, leucine, isoleucine, or phenylalanine as the hydrophobic stabilizer, an ordinary skilled artisan would have been motivated to try different amino acids as stabilizers; because JP-224 teaches that any amino acid is suitable and valine, leucine, isoleucine, or phenylalanine are among the 20 naturally occurring and common amino acids. Applicants have made no allegations of surprising or unexpected results in their specification. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The instant rejection is deemed to be proper.

Response to Arguments

Applicant's arguments filed April 21, 2009 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by attacking the references individually and arguing that (1) JP '826 does not teach or suggest the combination of hydrophobic amino acids and hydrophilic amino acids; and (2) the combined prior art does not suggest or provide motivation to combine both hydrophilic and hydrophobic amino acid stabilizers in the same freeze-dried composition.

The Examiner respectfully disagrees with Applicants' traversal arguments. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Regarding (1), JP '826 in fact does suggest the combination of hydrophilic and hydrophobic amino acids, as evidenced by the teachings of Akagi, the English language equivalent of JP '826. Regarding (2), in addition to the suggestion of Akagi to utilize two or more amino acid stabilizers, the ordinary skilled artisan would have been motivated to combine two known stabilizers, such as the hydrophobic (JP '826/Akagi) and hydrophilic amino acids (JP '826/Akagi and JP-224), because both are recognized as having a stabilizing effect on interferon-gamma compositions. The combination of two or more stabilizers would reasonably be expected to exhibit at least an additive stabilizing effect. It is generally considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the

prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). Thus, Applicants' traversal arguments are unpersuasive and the instant rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-61 of U.S. Patent No. 7,448,379 (USPN '379). Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim sets claim freeze-dried compositions characterized by the same properties and comprising, in some embodiments, overlapping carrier/stabilizer materials.

Independent claim 1 of the instant application was described above. Independent claim 28 of USPN '379 claims a non-powder-form freeze-dried composition for transpulmonary

administration comprising at least one active ingredient and having a disintegration index greater than or equal to 0.015, being characterized by becoming fine particles upon impact with air at a speed greater than or equal to 1 m/s at an air flow rate greater than or equal to 17 ml/s, wherein the fine particles have a mean particle diameter less than or equal to 10 microns of a FPF greater than 10%. Dependent claim 38 of USPN '379 depends directly from claim 28 and indicates that the composition comprises at least one carrier. The fact that dependent claim 38 utilizes "comprises" and not "further comprises" indicates that the claimed composition of claim 28 of USPN '379 inherently comprises one or more carriers. Suitable carriers are recited in dependent claim 39 of USPN '379 and include amino acids.

The primary difference between the claims of USPN '379 and the claims of the instant application is that the claims of USPN '379 do not specify that the active ingredient is interferon-gamma or that the carriers (e.g. amino acids) are necessarily a mixture of hydrophilic and hydrophobic amino acids. Looking to the specification of USPN '379 for a definition of carrier and amino acids and to ascertain which carriers/amino acids were within the scope of the general term, one finds the term amino acid to be inclusive of hydrophobic amino acids (e.g. valine, leucine isoleucine, etc.), hydrophilic amino acids (e.g. proline, alanine, arginine, glycine, etc.) and combinations thereof (see col. 17, line 66 through col. 18, line 33). Thus, the combination of hydrophobic and hydrophilic amino acids is an obvious modification of the composition claimed in USPN '379. The scope of the term active agent as used in USPN '379 is set forth from col. 16, line 66 through col. 17, line 50 and includes interferon-gamma. Thus, the selection of interferon-gamma as the active agent is an obvious modification of the composition claimed in USPN '379. The term "non-powder-form freeze-dried composition" is defined in col. 16, lines

3-6 of USPN '379 to mean "freeze-dried cake." It is proper to rely on a patent's or an application's disclosure as a dictionary and/or to understand the scope of what is meant by a term in a claim and as well as to ascertain what constitutes an obvious modification. This position is supported by the courts. See *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 1-14 *prima facie* obvious over claims 28-61 of U.S. Patent No. 7,448,379 (USPN '379.

Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 12/427,700 (filed April 21, 2009) (copending '700). Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim sets claim freeze-dried interferon-gamma transpulmonary compositions comprising (i) at least one hydrophobic stabilizer selected from hydrophobic amino acids, di- and tripeptides thereof, and derivatives thereof, (ii) at least one hydrophilic stabilizer selected from hydrophilic amino acids, di- and tripeptides thereof, and derivatives thereof, and (iii) gamma-interferon, wherein both sets of claimed compositions recite the same properties. The differences between the claims of the instant application and those of copending '700 are that the claims of copending '700 do not recite the specific derivatives of hydrophobic amino acids (e.g. L-isoleucyl-beta-naphthylamido hydrobromide or amides thereof). The differences between the two claim sets are considered obvious modifications, because the term derivative as used in copending '700

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1-14 are rejected. Claims 15-24 are withdrawn from consideration. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.H.A.-A.
Patent Examiner
Technology Center 1600

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616